Reply to Drs Ahern and Schnoor

To the Editor—Despite over 50 years of use, currently employed colistin dosing regimens may result in low serum peak concentration leading to suboptimal and delayed effective treatment. A higher single-dose and longer dosing interval...
strategy, along with a loading dose, as applied in our pilot study, seem effective and less toxic than expected [1].

However, we thank Drs Ahern and Schnoor [2] for their safety warning about colistin dosage. We fully agree that while dealing with the issue of dosing strategy, some clarifications are needed in order to avoid under- or over-dosing of colistin.

In our study, colistin was administered as colistimethate sodium (CMS; Coly-Mycin, 1 vial containing 1 million international units [IU]) at the dose of 9 million units (MU), followed by a maintenance dose of 4.5 MU every 12 hours. We are aware that in the United States, for example, colistin is given as Coly-Mycin, a formulation that, although containing CMS (ie, equal to our study), is expressed as mg (1 vial containing approximately 400 mg CMS), and is labeled as containing 150 mg colistin base activity (CBA) per vial. Moreover, the recommended daily and upper daily dose of the 2 formulations are different.

CMS is safer to administer parenterally because of its lower rate of toxicity. As a prodrug, CMS is hydrolyzed to form partially sulfomethylated derivatives, as well as colistin sulfate, the active form of the drug. Until colistin is formed, CMS by itself is considered an inactive prodrug of colistin and displays little to no antibacterial activity.

It has been established that there are approximately 12,500 IU per 1 mg CMS. Therefore, 1 MU Colomycin equals 80 mg Coly-Mycin. If we had to convert into milligrams, the dose of 9 MU CMS, followed by a maintenance dose of 4.5 MU every 12 hours used in our study, we should administer 720 mg CMS, followed by a maintenance dose of 360 mg every 12 hours.

Although Coly-Mycin contains CMS (ie, the safer form to administer), it is labeled in terms of CBA, but CMS and CBA cannot be used interchangeably, especially when dosing, because there are approximately 2.67 mg CMS per 1 mg colistin base [3].

Our loading dose of CMS would, therefore, be equivalent to approximately 270 mg CBA, and the maintenance dose would be equivalent to 135 mg CBA every 12 hours.

As far as the dose is concerned, the recommended maximum daily dose of Colomycin (6 MU, equivalent to 480 mg CMS) is almost half that of Coly-Mycin (5 mg/kg CBA, equivalent to approximately 13.3 mg/kg CMS) and, according to recent literature and our study, it would be less than optimal, particularly in view of pharmacokinetic/dynamic of colistin and of increasing threat from multidrug-resistant (MDR) bacteria.

Clearly, the multiplicity of terms used to express content of vials and dosage information has major potential for dosage error when administering “colistin” to patients or for confusion when comparing data collected from studies conducted in various parts of the world. The use of uniformed dosage form and unit would, moreover, greatly benefit the identification of colistin correct dosing.

While patients are dying of MDR gram-negative bacteria infections and colistin may be the only rescue therapy, its misuse can be fatal. We strongly call for an international consensus statement to uniform the labeled content of parenteral vials, the associated dosage unit, as well as the correct amount of colistin to be administered to patients.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References


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Clinical Infectious Diseases 2012;55(9):1275–6

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DOI: 10.1093/cid/cis633

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